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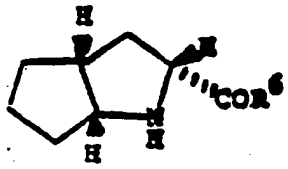
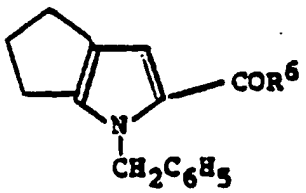
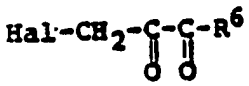
(54) Title: NOVEL PROCESS FOR THE PREPARATION OF CIS, ENDOOCTAHYDROCYCLOPENTA[b]PYRROLE-2-CARBOXYLATE



IIIa



II



V

(57) Abstract

Novel process for the preparation of cis,endo-octahydrocyclopenta[b]pyrrole-2-carboxylate (IIIa) wherein R^6 is hydroxy, lower alkoxy, lower alkenoxy, dilower alkylamino lower alkoxy, acylamino lower alkoxy, acyloxy lower alkoxy, aryloxy, arylloweralkoxy, amino, lower alkylamino, dilower alkylamino, hydroxyamino, aryllower alkylamino, or substituted aryloxy or substituted aryllower alkoxy wherein the substituent is methyl, halo or methoxy, which comprises catalytic reduction of compound (II), which further may comprise preparing the compound of formula (II) by the reaction of a halo pyruvate ester (V) with benzyliminocyclopentane. Compounds (IIIa) are useful intermediates for the preparation of certain ACE-inhibitors.

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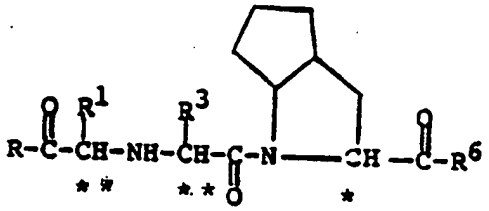
NOVEL PROCESS FOR THE PREPARATION OF CIS,ENDO-OCTAHYDROCYCLOPENTA[b]PYRROLE-2-CARBOXYLATE

Inhibitors of angiotensin-converting enzymes are useful in the treatment of cardiovascular disorders especially as antihypertensive agents and also in the treatment of congestive heart failure and of glaucoma. Such ACE-inhibitors have, for example, been described in the published European patent applications Nos. 50800 and 79022.

Of particular interest as ACE-inhibitors are compounds of the general formula (I)



I

and the pharmaceutically acceptable salts thereof, wherein R and R^6 are the same or different and are hydroxy, lower alkoxy, lower alkenoxy, diloweralkylamino lower alkoxy (e.g. dimethylaminoethoxy), acylamino lower alkoxy (e.g. acetylaminoethoxy),

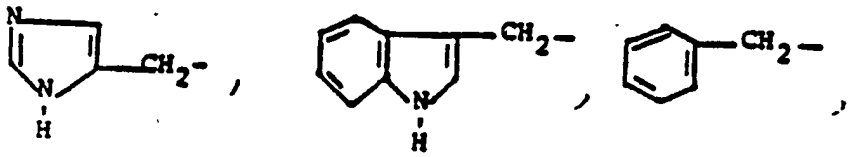
acyloxy lower alkoxy (e.g. pivaloyloxyethoxy), aryloxy (e.g. phenoxy), aryllowеralkoxy (e.g. benzyloxy), amino, lower alkylamino, diloweralkylamino, hydroxyamino, aryllower alkylamino (e.g. benzylamino), or substituted aryloxy or substituted aryllowеralkoxy wherein the substituent is methyl, halo or methoxy;

R^1 is hydrogen, alkyl of from 1 to 10 carbon atoms, including branched and cyclic and unsaturated (e.g. allyl) alkyl groups, substituted lower alkyl wherein the substituent is hydroxy, lower alkoxy, aryloxy (e.g. phenoxy), substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, amino, lower alkylamino, diloweralkylamino, acylamino, arylamino, substituted arylamino, guanidino, imidazolyl, indolyl, lower alkylthio, arylthio (e.g. phenylthio), substituted arylthio, carboxy, carbamoyl, lower alkoxycarbonyl, aryl (e.g. phenyl or naphthyl), substituted aryl, aralkyloxy, substituted aralkyloxy, aralkylthio, or substituted aralkylthio, wherein the aryl or heteroaryl portion of said substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkyloxy or aralkylthio groups is substituted with a group selected from halo, loweralkyl, hydroxy, lower alkoxy, amino, aminomethyl, carboxyl, cyano and sulfamoyl; and

R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethylphenyl lower alkyl, hydroxyphenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl (e.g. benzoylamino lower alkyl or acetylamino lower alkyl), amino lower alkyl, dimethylamino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, or lower alkylthio lower alkyl.

As used herein, acyl includes $-\overset{O}{\overset{\|}{C}}-R^{12}$ wherein R^{12} is low r alkyl, lower alk nyl or aryl. The lower

alkyl or lower alkenyl groups exc pt where noted otherwise are represented by any of the variables including straight and branched chain hydrocarbon radicals from one to six carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl or vinyl, allyl, butenyl and the like. Cycloalkyl groups include bridged and non-bridged groups. The aralkyl groups represented by any of the above variables have from one to four carbon atoms in the alkyl portion thereof and include for example, benzyl, p-methoxybenzyl and the like. Halo means chloro, bromo, iodo or fluoro. Aryl, where it appears in any of the radicals, except where noted, represents phenyl or naphthyl. Heteroaryl groups where they appear include for example pyridyl, thienyl, furyl, indolyl,benzothienyl, imidazolyl and thiazolyl. The R^1 and R^3 substituted lower alkyl moieties are exemplified by groups such as



$HO-CH_2-$, $HS-CH_2-$, $H_2N-(CH_2)_4-$, $CH_3-S-(CH_2)_2-$,

$H_2N-(CH_2)_3-$, $H_2N-\overset{\overset{NH}{\|}}{C}-NH-(CH_2)_3-$ and the like.

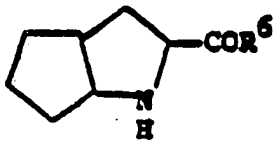
Preferred compounds of formula I are those in which R is hydroxy or lower alkoxy, R^1 is lower alkyl or substituted lower alkyl wherein the substituent is aryl, R^3 is lower alkyl or aminoloweralkyl and R^6 is hydroxy.

The aforementioned compounds of the formula I, as defined above, include all possible stereo-

isomers. Preferred stereoisomers are the cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acids, wherein preferably the absolute configuration at the carbon atoms marked by a double asterisk in the above formula I is most similar to that of natural L-amino acids, which usually are assigned the S-configuration. Particularly preferred compounds are 1-[N-(1(S)-carboxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]-pyrrole-2(S)-carboxylic acid, 1-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocycloyclopenta[b]pyrrole-2(S)-carboxylic acid, 1-[Nα-(1(S)-carboethoxy-3-phenylpropyl)-(S)-lysyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid, 1-[Nα-(1(S)-carboxy-3-phenylpropyl)-(S)-lysyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid, 1-[N-(1(S)-carboxybutyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid, 1-[N-(1(S)-carboethoxybutyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid, 1-[Nα-(1(S)-carboethoxybutyl)-(S)-lysyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid, and 1-[Nα-(1(S)-carboxybutyl)-(S)-lysyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid or their hydrochloride salts. A most preferred compound is 1-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2-(S)-carboxylic acid and its hydrochloride salt.

These compounds can be prepared by known methods such as described in the above mentioned European published patent applications Nos. 50800 and 79022.

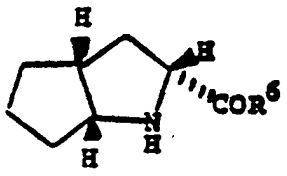
One of the starting materials for the preparation of compounds of formula I is octahydrocyclopenta[b]pyrrole-2-carboxylate, III,



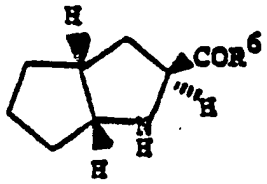
III

wherein R^6 is as defined above.

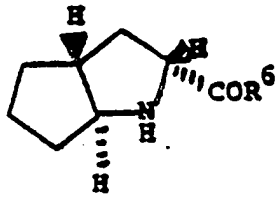
Compounds of formula III consist of eight stereoisomers composed of four racemic pairs; the two cis epimers, IIIa and IIIb, and the two trans epimers, IIIc and IIId:



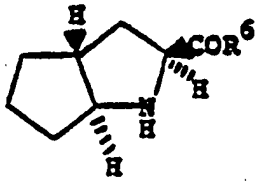
(±) IIIa



(±) IIIb



(±) IIIc



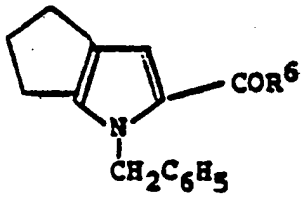
(±) IIId

As used herein, the formulae IIIa, IIIb, IIIc and IIId are meant to comprise the relevant racemic pair of optical isomers.

The compounds of formula III can be prepared by known methods, such as disclosed in the publications mentioned above, followed, if desired, by isolation of the racemic pairs of isomers or their individual component enantiomers according to resolution methods well described in the art.

The present invention provides a novel process for the preparation of the compounds of the

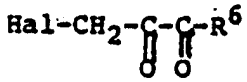
gen ral formula IIIa. This process compris s catalytic r duction of compound II



II

wherein R^6 is as defined above, followed, if desired by the resolution of the racemic mixture to obtain the individual enantiomer.

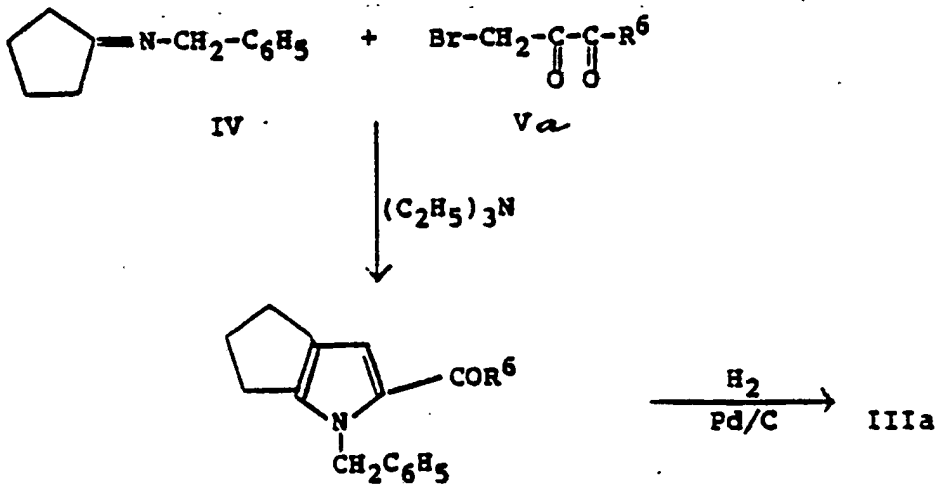
Compound II can be prepared by the reaction of a halopyruvate ester (V)



V

wherein R^6 is as defined above and Hal stands for halogen, with benzyliminocyclopentane.

This procedure can be exemplified by the following reaction scheme:



II

The process for preparing the novel compounds II (1-benzyl-1,4,5,6-tetrahydrocyclopentane[b]pyrrole-2-carboxylic acid or its esters) preferably uses a lower alkyl ester of bromo pyruvate (e.g. R^6 is ethoxy, methoxy or t-butoxy). Preferably, equimolar amounts of reactants are used. The reaction is carried out in an inert solvent such as, for example, an alcohol (e.g. ethanol), acetonitrile or dimethylformamide in the presence of a base such as, for example, triethylamine. The reaction may be carried out at from 0-100°C for 2-8 hours, but is preferably carried out at low temperatures (e.g. 0-5°C) for approximately 2 hours, then at reflux (temperature depends on solvent) for 2 hours.

The catalytic reduction of compound II to saturate the ring and remove the benzyl group is carried out in a solvent such as an alcohol (e.g. ethanol) in the presence of hydrogen gas and a catalyst such as $Pd(OH)_2$ on carbon, Pd on carbon or other appropriate catalysts. The resultant product may be isolated by methods well known to those skilled in the art, e.g. by treating with an acid such as HCl to prepare the salt, followed by removal of the salt (e.g. by basifying with sodium hydroxide) to obtain the compound of formula IIIa, followed, if desired by the isolation of the individual enantiomers.

In the above reactions, the group R^6 being other than hydrogen (especially aryllower alkyl) can be hydrogenolyzed to some extent. Consequently, an additional esterification step may be required to obtain the desired compound.

The above described process is stereospecific so that compounds IIIa (cis,endo-form) are obtained directly. These compounds are useful in the

preparation of the preferred compounds of formula I (listed above) which are also the cis,endo-isomers. This is a great advantage over the known method for preparing compounds of formula III which are not stereospecific so that additional process steps have to be carried out to isolate the desired isomer of the intermediate (III) or of the end product (I). Compounds IIIa as obtained by this process are racemic mixtures. The individual enantiomers can be obtained by conventional resolution methods well described in the art, such as fractional crystallization of appropriate diastereomeric salts, for example the fractional crystallization of compounds IIIa wherein R^6 is benzyloxy or its benzyloxycarbonyl-L-phenylalanine salt.

The compounds of formulae IIIa (cis,endo-form) can be converted to the corresponding compounds having the cis,exo-form (IIIb). Such epimerizations are most conveniently carried out on the free base ester forms of these compounds, in the absence or presence of additional basic catalysts such as potassium t-butoxide, triethylamine and the like.

The following examples illustrate the process of this invention, the preparation and use of the compounds of the present invention. The diasterioisomers prepared as set forth below may be isolated by column chromatography or by fractional crystallization.

EXAMPLE 1

ETHYL CIS,ENDO-OCTAHYDROCYCLOPENTA[b]PYRROLE-2-CARBOXYLATE

A. Ethyl 1-Benzyl-1,4,5,6-Tetrahydrocyclopenta-[b]Pyrrole-2-Carboxylate.

Add dropwise 3.9 gm of ethyl bromopyruvate in 50 ml of ethanol to a flask containing 3.46 gm of benzyliminocyclopentane and 2.0g of triethylamine in 50 ml of ethanol at 0°C, stir for 2 hours, then heat to reflux for 2 hours. Concentrate the reaction mixture and partition between 1N HCl and ether. Dry the ether extract over magnesium sulfate, filter, concentrate under high vacuum to obtain a brown oil and distill in a kugelrohr at 190-210°/0.1 mm to obtain the title compound of Part A as a yellow oil.

B. Ethyl Cis,Endo-octahydrocyclopenta[b]pyrrole-2-Carboxylate Hydrochloride.

Introduce hydrogen gas to a mixture of 2.3 gm of the pyrrole compound produced in part A of this Example and 1.5 gm of 20% $Pd(OH)_2/C$ in 200 ml of ethanol, and stir the reaction mixture. After 24 hours add an additional 0.8 gm of the palladium catalyst. After 600 ml of hydrogen gas is absorbed, filter the reaction mixture and concentrate to obtain a liquid and a solid. Take up the liquid in ether and filter. Treat the filtrate with 2.86N HCl/ether to obtain an oil which solidifies. Filter off the solid to obtain the hydrochloride salt of the title compound of Part B as a beige solid, m.p. 163°-7°C. Recrystallization from CH_2Cl_2 and hexane raises the melting point to 171°-2°C.

C. Cis,Endo-Octahydrocyclopenta[b]pyrrole-2-Carboxylic Acid.

Stir a mixture of 10.7 g of ethyl cis,endo-octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride (from Part B above) and 175 ml of 1N sodium hydroxide at room temperature for 20 hours and then concentrate in vacuo. Place the residue on a silica gel (1000 g, 60-200 mesh) column and elute with chloroform:isopropanol:7% ammonium hydroxide 1:1:1 (organic layer) to give cis,endo-octahydrocyclopenta-[b]pyrrole-2-carboxylic acid, as a white solid, m.p. 220-222°C; TLC: R_f 0.12 (0.25 mm silica; $CHCl_3$:isopropanol:7% NH_4OH-1:1:1-lower phase); MS: 156, 155 (M^+), 126 (M-HCO), 111 (M-CO_2), 110 (M-CO_2H; 100%), 93 [M-H$(CH_2)_3$], 82 (M-CH_2=$CHCO_2H$), 80 (M-H_2,CH_2=$CHCO_2H$), 68 [M-CO_2H, $(CH_2)_3$], 67 [M-HCO_2H,$(CH_2)_3$].

NMR (400 MHz-D_2O); δ 4.39 (1H doublet of doublets J=11Hz,8Hz); 4.20 (1H multiplet); 3.00 (1H multiplet); 2.66 (1H multiplet); 2.03-1.78 (6H multiplet); 1.57 (1H multiplet).

EXAMPLE 2

1-[N-(1(R,S)-CARBOETHOXY-3-PHENYLPROPYL)-(S)-ALANYL]-CIS,ENDO-OCTAHYDROCYCLOPENTA[b]PYRROLE-2(S)-CARBOXYLIC ACID

A. To a solution of 10.0 g of ethyl-cis,endo-octahydrocyclopenta[b]pyrrole-2-carboxylate in 400 ml of ethyl acetate add 17.0 g of N-benzyloxycarbonyl-(S)-alanine, N-hydroxysuccinimide ester. Stir the reaction mixtur at room temperature for 20 hours and conc n-

trat it in vacuo. Plac the residu on a column of silica gel (3000 g, 60-200 mesh) and elute with chloroform:ethyl acetate 10:1 to obtain 1-[N-benzyloxy-carbonyl-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]-pyrrole-2-carboxylic acid, ethyl ester, a colorless oil $[\alpha]_D^{26}$-32.6° (C = 0.5, ethanol).

B. To a solution of 3.22 g of 1-[N-benzyloxy-carbonyl-(S)-alanyl]-cis,endo-octahydrocyclopenta-[b]pyrrole-2-carboxylic acid, ethyl ester in 150 ml of methanol, add 20 ml of 2.5 N sodium hydroxide and stir the mixture at room temperature for 18 hours. Concentrate the mixture under nitrogen, dilute the residue with ice-water and then make the mixture acidic with concentrated hydrochloric acid. Extract the aqueous solution with ethyl acetate and dry the organic phase over magnesium sulfate. Concentrate the organic phase and place it on a column of silica gel (500 g., 60-200 mesh). Elute with chloroform:glacial acetic acid 9:1 and isolate 1-[N-benzyloxycarbonyl-(S)-alanyl]-cis,endo-octahydrocyclo-penta[b]pyrrole-2(S)-carboxylic acid, as a colorless oil, $[\alpha]_D^{26}$-26.4° (C = 0.5, ethanol).

C. Dissolve 1.70 g of 1-[N-benzyloxycarbonyl-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid in 100 ml of methanol. Add 0.40 g 10% palladium-on-charcoal and hydrogenate the mixture at atmospheric pressure. Filter the mixture and concentrate in vacuo to obtain 1-[(S)-alanyl]-cis,endo-octahydro-cyclopenta[b]pyrrole-2(S)-carboxylic acid.

D. Dissolve 1-[(S)-alanyl]-cis,endo-octahydro-cyclopenta[b]pyrrole-2(S)-carboxylic acid in 100 ml of

absolute methanol. Add 1.10 g 2-oxo-4-phenylbutyric acid, ethyl ester and 20 ml of 3 Angstrom molecular sieve pellets, and stir the resulting mixture at room temperature for eighteen hours. Filter the reaction mixture and treat the filtrate with 0.68 g sodium cyanoborohydride at room temperature for two hours. Concentrate the mixture under nitrogen and dilute the oil with dilute hydrochloric acid and stir at room temperature for one hour. Absorb the aqueous solution on 200 ml of a XAD-2 (Rohm & Haas Co. resin). Elute the resin with 2000 ml of water and then with 2000 ml of methanol. Concentrate the methanol solution and place the residue on a column of silica gel (400 g, 60-200 mesh) and elute with chloroform:isopropanol:7% ammonium hydroxide (1:1:1) (organic layer) to give 1-[N-(1(R,S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid, as a colorless oil, $[\alpha]_D^{26}$ -5.8° (C=10.6, ethanol).

EXAMPLE 3

1-[N-(1(S)-CARBOETHOXY-3-PHENYLPROPYL)-(S)-ALANYL]-CIS,ENDO-OCTAHYDROCYCLOPENTA[b]PYRROLE-2(S)-CARBOXYLIC ACID AND THE HYDROCHLORIDE SALT THEREOF

Method I

A. Cis,endo-Octahydrocyclopenta[b]pyrrole-2-Carboxylic Acid Hydrochloride

Method I Add a 20% HCl in dioxane solution (100 ml) to 5 g. of cis,endo-octahydrocyclopenta[b]pyrrole-2-carboxylic acid. Stir the resulting mixture at room temperature for 30 min. and then concentrate it in vacuo. Wash the white residue with anhydrous ether and dry in vacuo to obtain

the title compound of Part A as a white solid, m.p. 209-211°.

Method II Dissolve 0.2 g of ethyl cis,endo-octahydrocyclopenta[b]pyrrole-2-carboxylate (free base or hydrochloride from Example 1 in 20 ml of 6N hydrochloric acid and reflux overnight. Cool the reaction mixture, remove the volatiles under high vacuum and obtain the title product of Part A.

B. To 5.0 g of the product of Part A, add 50 ml of benzyl alcohol and 50 ml of thionyl chloride and stir at room temperature. Concentrate the reaction mixture in vacuo and recrystallize the residue from chloroform/ isopropanol to give benzyl cis,endo-octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride, m.p. 175°.

C. To 5.5 g of the product of Part B, add 2.6 g of 1-hydroxybenzotriazole, 5.4 g of N[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanine and 4.0 g of dicyclohexyl-carbodiimide in 80 ml of dimethyl formamide. Stir the reaction mixture at room temperature for 18 hours. Filter the reaction mixture, and add ethyl acetate to the filtrate. Extract the ethyl acetate solution (3 X 200 ml) with 5% aqueous sodium bicarbonate. Concentrate the dried ($MqSO_4$) ethyl acetate solution in vacuo. Chromatograph the residue on a silica gel column (400 g, 60-200 mesh) and elute with ethyl acetate/petroleum ether (30-60°) 2:1. Isolate, as the first eluted material, 1-[N-(1(S)-carboethoxy-3-

phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocycl - penta[b]pyrrole-2(S)-carboxylic acid benzyl ester.

D. Hydrogenate 3.0 g of 1-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid benzyl ester in 40 ml of ethanol containing 0.5 g of 10% Pd/C. Remove the catalyst by filtration and concentrate the filtrate in vacuo. Add absolute ether to crystallize 1-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocyclo penta[b]pyrrole-2(S)-carboxylic acid, m.p. 110-112°C(d).

E. Add dropwise, with stirring, a solution of 1.3 M hydrochloric acid in ether to the product of Part D until the mixture is pH2. Add 100 ml of ether and continue to stir for 30 minutes, then filter to obtain 1-[N-1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid hydrochloride.

Method II

A. Stir a solution of 4.56 g of N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanine, 2.20 g of N-hydroxy-succinimide and 3.80 g of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride in 30 ml of dimethyl-formamide for 18 hours at room temperature. Dilute the reaction mixture with ethyl acetate and wash the ethyl acetate layer with saturated aqueous sodium chloride. Concentrate the dried ($MqSO_4$) ethyl acetate solution to give N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanine N-hydroxysuccinimide ester.

B. To a mixture of 3.76 g of the product of Part A and 1.55 g of cis,endo-octahydrocyclopenta[b]-pyrrole-2-carboxylic acid in 30 ml of dimethylformamide, add 1.5 ml of triethylamine and stir the resulting mixture at room temperature for 18 hours. Concentrate the reaction mixture in vacuo and partition between ethyl acetate and H_2O (adjusted to pH 4). Wash the ethyl acetate solution with saturated aqueous sodium chloride. Concentrate the dried ($MgSO_4$) ethyl acetate solution in vacuo and chromatograph the residue on a silica gel (1000 ml) column using 1:1:1 $CHCl_3$/iso-PrOH/7% NH_4OH (organic phase). Isolate 1-[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid as a foam.

EXAMPLE 4

ETHYL CIS,EXO-OCTAHYDROCYCLOPENTA[b]PYRROLE-2-CARBOXYLATE

Dissolve 0.4g of ethyl cis,endo-octahydrocyclopenta[b]pyrrole-2-carboxylate (as prepared in Example 1) in 40 ml of ethanol and 7 ml of triethylamine. Reflux under nitrogen for five days. Remove the volatiles in vacuo and isolate. To obtain the hydrochloride salt of the product of this example, treat the free base with ethereal HCl.

EXAMPLE 5

1-[N-(1(S)-CARBOXY-3-PHENYLPROPYL)-(S)-ALANYL]-CIS, ENDO-OCTAHYDROCYCLOPENTA[b]PYRROLE-2(S)-CARBOXYLIC ACID AND THE HYDROCHLORIDE SALT THEREOF

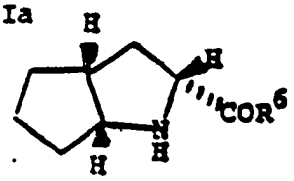
A. To a solution of 0.80g of 1[N-(1(S)-carboethoxy-3-phenylpropyl)-(S)-alanyl]-cis,endo-

octahydrocyclopenta[b]pyrrole-2(S)-carboxylic acid from Example 3 in 100 ml of methanol at 0-5°C, add 2.0 ml of 2.5N sodium hydroxide solution and stir at room temperature for 24 hours. Concentrate this solution in vacuo and absorb on 350 ml of AG50W-X2 Bio-Rad resin (100-200 mesh, hydrogen form). Wash the column with water until the eluate is neutral and elute the product with pyridine:H_2O (1:24). Concentrate the eluate in vacuo and chromatograph on a Lobar RP-8, size B column (E. Merck) using acetonitrile:water (2:3) as eluant to obtain the title compound of this example as the free amino acid.

B. Treat an ethanol solution of the product of Part A with one equivalent of a 1N solution of ethanolic hydrogen chloride. Remove the solvent in vacuo at room temperature to obtain the hydrochloride salt of the title compound of this example.

Claims

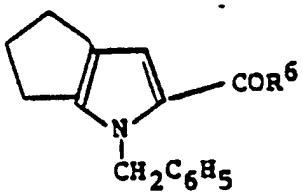
1. Process for the preparation of compounds of the general formula IIIa



IIIa

in the form of the racemic pair or of the individual enantiomers,

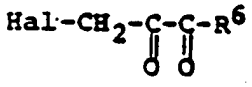
wherein R^6 is hydroxy, lower alkoxy, lower alkenoxy, dilower alkylamino lower alkoxy, acylamino lower alkoxy, acyloxy lower alkoxy, aryloxy, arylloweralkoxy, amino, lower alkylamino, dilower alkylamino, hydroxyamino, aryllower alkylamino, or substituted aryloxy or substituted aryllower alkoxy wherein the substituent is methyl, halo or methoxy, which comprises catalytic reduction of compound II



II

wherein R^6 is as defined above, followed if desired by the resolution of the racemic mixture to obtain the individual enantiomers.

2. Process according to claim 1, which further comprises preparing the compound of formula II by the reaction of a halo pyruvate ester (V)



V

wherein R^6 is as defined above and Hal stands for halogen, with benzyliminocyclopentane.

3. Process according to claim 1 or 2 comprising carrying out the reduction in a solvent, using hydrogen gas and $Pd(OH_2)$ on carbon or Pd on carbon.

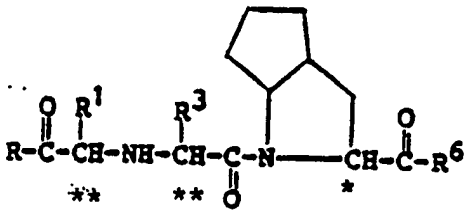
4. Process according to claim 3 comprising carrying out the reduction step in an alcohol.

5. Process according to any one of claims 2 to 4 comprising carrying out the reaction of the halo pyruvate ester with benzyliminocyclopentane in an inert solvent in the presence of a base at 0-100°C for about 2-8 hours.

6. Process according to any one of claims 2 to 5 comprising the use of bromo pyruvate ester (V).

7. Process according to any one of claims 1 to 6 comprising the isolation of compound IIIa in the free form or in the form of its ethyl or benzyl ester.

8. Us of compound (IIIa) obtained according to any one of claims 1 to 7 for the preparation of a cis,endo-octahydrocyclopenta[b]pyrrole-carboxylic acid derivative of general formula (I).



I

wherein R^6 is as defined above, R is defined as R^6,

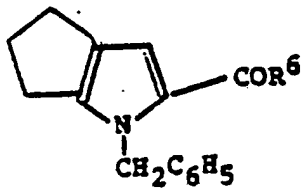
R^1 is hydrogen, alkyl of from 1 to 10 carbon atoms, including branched and cyclic and unsaturated alkyl groups, substituted lower alkyl wherein the substituent is hydroxy, lower alkoxy, aryloxy substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, amino, lower alkylamino, diloweralkyl-amino, acylamino, arylamino, substituted arylamino, guanidino, imidazolyl, indolyl, lower alkylthio, arylthio substituted arylthio, carboxy, carbamoyl, lower alkoxycarbonyl, aryl, substituted aryl, aralkyloxy, substituted aralkyloxy, aralkylthio, or substituted aralkylthio, wherein the aryl or heteroaryl portion of said substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkyloxy or aralkylthio groups is substituted with a group selected from halo, loweralkyl, hydroxy, lower alkoxy, amino, aminomethyl, carboxyl, cyano and sulfamoyl;

R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethylphenyl lower alkyl, hydroxyphenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl, amino lower alkyl, dimethylamino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, or lower alkylthio low r alkyl,

and wherein preferably the absolute configuration at the carbon atoms marked by a single asterisk in the above formula I is the S-configuration, and at the carbon atoms marked by a double asterisk are most similar to that of natural L-amino acids.

9. Use of compound (IIIa), preferably the S, S, S-form, according to claim 8 for the preparation of 1-[N-(1(S)-carboethoxy-3- phenylpropyl)-(S)-alanyl]-cis,endo-octahydrocylopenta- [b] pyrrole-2(S)-carboxylic acid.

10. Compound of formula II



II

wherein R^6 is as defined above.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/01406

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 209/52; C 07 K 5/06; A 61 K 37/02; A 61 K 31/04

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 209/00 C 07 K 5/00 A 61 K 37/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,Y	EP, A, 0084164 (HOECHST) 27 July 1983, see title page, pages 1-21,27-28,29-33, 35-36,38,41-42,44,46,48-50,53,56,62,65, 67,69-70,72-73,77-90	1,3-10
X	EP, A, 0079022 (HOECHST) 15 May 1983, see the whole document (cited in the application)	1-9
Y	EP, A, 0090362 (HOECHST) 5 October 1983, see title page; pages 1-18,54-61	1-2,8-9
P,Y	EP, A, 0135181 (HOECHST) 27 March 1985, see title page; pages 1-20	1-2,8-9
X	EP, A, 0050800 (SCHERING) 5 May 1982, see title page; pages 1-26,72-95 (cited in the application)	1-9
P,X	EP, A, 0115345 (HOECHST) 8 August 1984, see the whole document	1-10
P,X	EP, A, 0126986 (HOECHST) 5 December 1984, see title page; pages 1-15,26-29	1-10

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th October 1985	20 NOV. 1985
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruisberg

Form PCT/ISA/210 (second sheet) (January 1985)

International Application No. PCT/US 85/01406

III. DOCUMENTS C NSIDERED TO BE RELEVANT (CONTINUED FROM THE SEC ND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
P,X	EP, A, 0116842 (BOEHRINGER) 29 August 1984, see title page; pages 1-12,26-31 --	1-10
A	EP, A, 0084941 (I.C.I.) 3 August 1983, see title page; pages 1-20,71-80	8

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 85/01406 (SA 10302)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/11/85

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	9193182	07/07/83
		DE-A-	3210701	06/10/83
EP-A- 0079022	18/05/83	DE-A-	3226768	26/05/83
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		US-A-	4528282	09/07/85

INTERNATIONAL APPLICATION NO. PCT/US 85/01406 (SA 10302)